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Pharmacogenetics and Practice: Tailoring Prescribing for Safety and Effectiveness

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Introduction

The promise of pharmacogenomics testing, to find the right medication at the right dose for the right patient at the right time, sits at the heart of precision medicine. Identifying genetic variants that contribute to inter-patient variability in drug disposition and effect allows clinicians to select a more appropriate medication for a patient's condition by limiting adverse drug events and maximizing beneficial effects. However, as pharmacogenomics is increasingly integrated into prevention-based healthcare, a major obstacle to effective implementation of pharmacogenomics testing is the lack of adequate knowledge of healthcare providers on interpretation of these test results [1, 2].

A second barrier to effective implementation of pharmacogenomics testing is the cost associated with testing, which is not universally covered on a preventative basis.

Comprehensive, multigene panels are more cost-effective than multiple instances of single-gene targeted testing over a patient's lifetime [3] and give providers an opportunity to assess the risk of adverse drug reactions for a patient's current and future medications.

Pharmacogenetic testing is not routinely covered by insurance without prior authorization. The testing discussed in each of the following clinical vignettes was provided free to each patient. This pharmacogenetic testing is funded through multiple initiatives including a pragmatic clinical trial. Outside of these initiatives, the cost of pharmacogenetic testing varies widely depending on payer coverage and university subsidies.

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Clinicians understand that patients respond differently to identical treatments. Family history has long served as a source of genetic information. To provide some background, both drug-gene and drug-drug interactions (DDIs) may contribute to this variability. Drug-gene interactions often result from genetic variability in drug disposition enzymes. The major drug metabolizing enzymes are those that belong to the cytochrome P450 (CYP) superfamily, which accounts for the metabolism of 70–80% of clinically-used medications [4]. Genetic variants in genes coding for these CYP enzymes can alter enzyme function causing decreased or increased plasma concentrations of medication and lead to loss of beneficial effect or increase the risk for adverse effects.

To assist with interpretation of test results, the Clinical Pharmacogenetics Implementation Consortium (CPIC®) (<https://cpicpgx.org/>) and the Dutch Pharmacogenetics Working Group (DPWG) provide guidelines, with dosing recommendations for clinically actionable pharmacogenetic (genetic variants in one or few genes as opposed to the entire genome) test results. Refer to Supplemental Table 1: Comparison of the Clinical Pharmacogenetics Implementation Consortium (CPIC®) and the Dutch Pharmacogenetics Working Group (DPWG). (Note to printer: put this Supplemental Table 1 online only.). The predicted phenotypes are classified as poor, intermediate/reduced, extensive, rapid, or ultra-rapid and can be deduced from the presence of genetic variants (alternative alleles). This predicted phenotype is the individual's "metabolizer status." The guidelines use an asterisk-based nomenclature, where *1 is often the reference allele and assigned based on an individual lacking the alternative allele. The reference allele is (typically) used to refer to "normal" (not increased, decreased or altered) function of the drug metabolizing enzyme.

Many prescribed medications are substrates, inhibitors, and inducers of CYP enzymes. Substrates bind (interact) to CYP enzymes and are converted into active or inactive forms (metabolites). Sometimes, the administered medication is an inactive prodrug, which requires conversion to active form by the CYP system to convey its therapeutic effect. Inhibitors are medicines/compounds that decrease the function of the CYP enzyme, while inducers increase the function (Table 1). A list of common CYP substrates, inhibitors, and inducers are listed at <http://medicine.iupui.edu/clinpharm/ddis/main-table/>. Certain medicines can be categorized as having more than one effect (e.g. fluoxetine is a substrate and inhibitor).

As pharmacogenomics knowledge accumulates [5], healthcare institutions have implemented genotype-guided therapy in clinical practice. For example, the Indiana Genomics Implementation: An Opportunity for the Underserved (INGENIOUS) Trial [6–8] is currently underway at two major healthcare institutions: a safety net health system and a major university health system. Individuals that receive a first prescription, for one of the medications (with known guidelines regarding pharmacogenetic testing), were identified electronically as being trial eligible. They were contacted to enroll and after consenting, they were either randomized to the non-genotyping arm or randomized to the genotyping arm and tested.

Although the benefit of pharmacogenetic testing would be most significant if all patients are tested using a multigene panel prior to prescription of medications, this is challenging in the

situation where testing is costly and not covered by insurance. In such a setting, healthcare providers need to be able to assess which individuals would benefit from pharmacogenetic testing instead of testing all individuals or individuals based on receiving a prescription for a particular medication. Being able to identify those patients who would benefit the most from testing due to concerns about inefficacy or toxicity is particularly important in resource-constrained environments. The INGENIOUS trial involves healthcare providers, including advanced practice nurses (APNs), who provide primary and specialty care, requiring these providers to interpret test results. APNs are perfectly positioned in both settings to apply test results within the clinical context. By becoming familiar with these results, the lack of knowledge among clinicians can slowly be overcome [1, 9, 10].

The aims of this paper are to demonstrate (1) the benefit of pharmacogenetic testing and (2) the aspects involved with interpretation and application of results in a case-based manner. The three clinical vignettes below exemplify the benefits and complexities of pharmacogenetic-guided therapy in clinical practice. Table 2 includes a synopsis of the pertinent drug-gene and DDIs discussed in these clinical vignettes. A copy of a sample de-identified pharmacogenetics report can be found in the supplement material at <https://ascpt.onlinelibrary.wiley.com/doi/abs/10.1002/cpt.347>

Vignettes

The vignette illustrates how pharmacogenetic testing can be used as rationale for caregivers and payers to provide coverage for a necessary alternative medication to benefit a medically underserved person. Clopidogrel is used to inhibit platelet activation following PCI. It is a prodrug that is converted to an active metabolite (activated) by CYP2C19 in the liver. Compared to clopidogrel, the contribution of CYP2C19 in metabolism of ticagrelor and prasugrel is minor and, therefore, exposure to ticagrelor and prasugrel is influenced less by genetic variation in *CYP2C19*.

Ticagrelor and prasugrel are more expensive than clopidogrel. Some payers may be reluctant to reimburse the cost of these clopidogrel alternatives as first line therapy. When provided genetic information as justification, the insurer approved the use of ticagrelor in this situation.

Several studies have evaluated the efficacy of genotype-guided selection of antiplatelet therapies [12, 13]. Cost-effectiveness simulations tend to compare three scenarios: (1) universal clopidogrel use, (2) universal ticagrelor use, and (3) genotype-guided selection [12]. Although payers prioritize findings from randomized controlled trials ahead of retrospective studies [14], the potential cost of rehospitalization due to adverse events provides incentive to act on genetic information.

The tricyclic antidepressant (TCA), amitriptyline, is often prescribed for depression, anxiety, obsessive-compulsive and bipolar disorders, and neuropathic pain at doses starting at 10 mg to a maximum of 300 mg daily. For migraine and headache prevention, 10 mg amitriptyline is initially prescribed with the goal of increasing doses to 25 or 30 mg daily [15]. In this case, amitriptyline was prescribed for refractory left temporal headaches instead of NSAIDs

because of a likely DDI with warfarin that could result in bleeding and gastric mucosal damage [16]. Amitriptyline is mainly metabolized by CYP2C19 to nortriptyline that is also pharmacologically active, while CYP2D6 is responsible for metabolism of both amitriptyline and nortriptyline to less active hydroxy-metabolites (i.e. hydroxyamitriptyline and hydroxynortriptyline) [17]. Genotype-informed recommendations consider genetic variants in both *CYP2C19* and *CYP2D6* because CYP2C19 activity impacts the ratio of amitriptyline to nortriptyline while CYP2D6 has a larger influence on overall drug clearance. Her reduced CYP2D6 activity in addition to further inhibition of CYP2D6 by diphenhydramine or escitalopram could, in combination with a dose escalation to 30 mg daily, put her at risk of toxicity [18].

Warfarin, a widely prescribed anticoagulant, functions by inhibiting the activity of VKORC1, a major component of the vitamin K-dependent prothrombin clotting pathway. Too little inhibition of VKORC1 places the patient at risk of thrombosis, and too much inhibition increases the risk of major bleeding events. Consequently, warfarin has a narrow therapeutic window that requires regular monitoring of the patient's International Normalized Ratio (INR) of prothrombin time (PT).

Common genetic variants in *VKORC1* alter a patient's sensitivity to warfarin resulting in patients that are more sensitive to warfarin and require a lower dose to achieve therapeutic targets. CYP4F2 acts as a counterpart to VKORC1 by removing vitamin K from the vitamin K pathway and limiting excessive accumulation of vitamin K. Although genetic alterations in *CYP4F2* are associated with warfarin dose changes, the influence is smaller than that of variants in *VKORC1* [19]. The principal route of metabolism for S-warfarin occurs through CYP2C9, while R-warfarin is metabolized by CYP3A4 with minor contribution from CYP2C8, CYP1A1, CYP1A2, CYP2C18, and CYP2C19. Since S-warfarin is the more potent inhibitor of the vitamin K epoxide reductase complex, genetic variants of *CYP2C9* result in reduced metabolism of S-warfarin and increased risk of over-anticoagulation (i.e. bleeding events).

The vignette demonstrates the accuracy of genotype-guided warfarin dosing strategies. The patient presented with an existing prescription for a warfarin maintenance dose that was empirically (without genetic testing) determined. Genotype-guided dosing incorporates the patient's genotype (according to www.WarfarinDosing.org) and warrants a maintenance dose of 1.8 mg per day, or approximately 36% of the normal dose of 5 mg. In this case, the patient was titrated appropriately to alternating doses of 1–2 mg daily. Had the patient received pharmacogenetic testing prior to her initial warfarin prescription, it is possible her time to a therapeutic INR would have been reduced.

Pharmacogenetic testing is expected to improve efficacy in patients with depression, who typically respond to their first treatment only half of the time [20, 21]. CYP2D6 and CYP2C19 are responsible for metabolizing TCAs, most SSRIs, and half of all antipsychotics. Testing improves responder rates and tolerability [21] and may decrease the number of reported adverse events while increasing overall functioning [20]. Venlafaxine is a SNRI that is well-absorbed in the intestines and extensively metabolized by CYP2D6 in the liver, with minor involvement of CYP2C19.

Venlafaxine requires a strict dosing regimen to maintain therapeutic concentrations. Approximately 80% of patients have *CYP2D6* variants, resulting in increased or decreased CYP2D6 activity [2]. DPWG guidelines for individuals with reduced activity of CYP2D6 recommend the selection of an alternative medicine not metabolized by CYP2D6 [22]. Therefore, the prescriber in the third vignette discontinued venlafaxine and prescribed an alternative not metabolized by CYP2D6.

Conclusion

Available pharmacogenetic testing can already benefit individual patients; however, APNs and other providers experience significant challenges when implementing such testing. As more pharmacogenetic or pharmacogenomic studies are performed, the data and evidence are evolving rapidly. Providers are encouraged to make treatment decisions based on the highest quality evidence at the time and not use pharmacogenetic testing when the benefit is not known.

Efforts are currently underway to harmonize CPIC and DPWG guidelines, but providers should note that differences exist. In addition to providing a straightforward example of pharmacogenetic implementation, the third clinical vignette illustrates a notable difference between CPIC and DPWG guidelines. Currently no primary evidence exists linking altered metabolism of venlafaxine to *CYP2D6* variants, therefore, CPIC has not issued any guidelines for this drug-gene combination. DPWG, in contrast, provides guidelines based on drug-gene interactions of existing medications, which associates variants resulting in less active CYP2D6 with decreased efficacy of venlafaxine. It is well-established that *CYP2D6* is the most variable member of the *CYPs* and studies demonstrate altered drug metabolism due to *CYP2D6* variants. This facilitates DPWG to extend general guidelines for other medicines metabolized by CYP2D6 to venlafaxine.

Reimbursement for pharmacogenetic testing, using single-gene tests, generally occurs under a reactive ordering approach, meaning that a patient is tested before a high-risk prescription or in response to adverse events [14]. The INGENIOUS study broadens the cost-effectiveness and impact of reactive testing by using the same multigene panel for all patients enrolled in the study, regardless of the medication that prompted enrollment. Because of the wide inclusion criteria, patients often present with multiple current medications and comorbidities. Given the frequency of actionable genetic variants, the multigene panel approach routinely identifies findings unrelated to the medication which prompted the trial team to contact the patient regarding enrollment. These findings may include actionable genetic variants for medications the patient is not currently taking yet might be prescribed in the future. Other times drug-gene interactions are relevant to current medications.

Every patient presents a unique challenge to the pharmacogenetic interpretation of his or her case. This makes it difficult to automate interpretation of test results and requires a knowledgeable provider to assess each patient's genotype and medications. In these clinical vignettes, we presented examples of pharmacogenetic testing that required nuanced interpretation of drug-gene and DDIs. Pharmacogenetic test interpretation should not be

confined to the medication of interest; it is also necessary to assess drug-gene interactions of existing medications to explain symptoms, inform selection of alternative treatment options, and improve efficacy of the patient's medication profile. With sufficient knowledge and experience, APNs will become more confident in applying pharmacogenetic results within the clinical context.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Highlights

1. APNs are crucial for the effective implementation of precision medicine
2. Drug-gene and drug-drug interactions present patient-specific challenges
3. Two sets of guidelines assist with interpretation and patient recommendations
4. With sufficient knowledge and experience, APNs can apply pharmacogenetic results

Clinical vignette 1: clopidogrel

A 50-year-old Hispanic man presented to the emergency department with chest pain radiating to the left arm, diaphoresis, and shortness of breath. An electrocardiogram demonstrated anterior ST elevation myocardial infarction (STEMI) with significant 3-vessel coronary artery disease. He underwent percutaneous coronary intervention (PCI) and placement of a bare metal stent. He was started on the anticoagulant, ticagrelor, 90 mg twice daily plus aspirin (324 mg and then 81 mg daily). His lack of health insurance coverage necessitated that he be switched to clopidogrel a month later because the cost for 90 days of treatment with clopidogrel would be \$8.84 while the comparable treatment with ticagrelor would be \$175.97.

The order for clopidogrel prompted patient contact to enroll in the trial, randomization to the genotyping arm and pharmacogenetic testing. The patient's test result revealed he has the *CYP2C19* *17/*17 genotype. Clopidogrel is converted to active form by CYP2C19. Having two gain of function alleles (*17) predicts that he has increased CYP2C19 metabolic activity. As a result, he is at higher risk of bleeding when prescribed clopidogrel [11].

Following discussion with his health insurance providers and care team, the patient was maintained on treatment with ticagrelor plus aspirin. He reported no chest pain, no significant fatigue after walking, absence of diaphoresis, and no symptoms or signs of bleeding at his 1-month follow-up visit. For this patient, pharmacogenetic testing provided support for treatment based on both his clinical and genetic factors.

Clinical vignette 2: amitriptyline and warfarin

A 66-year-old White woman with a history of hypertension, restless legs syndrome, and fibromyalgia received a prescription for amitriptyline for refractory left temporal headaches. This medication order prompted the trial team to contact the patient regarding enrollment, which resulted in pharmacogenetic testing. She has a history of two separate episodes of a pulmonary embolus and deep venous thrombosis for which she is on life-long anticoagulation with warfarin.

For her headaches, she was initially prescribed 10 mg amitriptyline at night with a goal dose of 30 mg. Additional medications included; 50 mg diphenhydramine daily, 10 mg escitalopram daily, and alternating doses of 1 mg and 2 mg warfarin daily.

Pharmacogenetic testing revealed the following genotypes: *CYP2C19* *1/*1, *CYP2D6* *4/*41, *CYP2C9* *2/*3, *VKORC1* rs9923231 (c.-1639G>A) A/A, and *CYP4F2* *1/*3. Amitriptyline is metabolized by *CYP2C19* and *CYP2D6*. Although the patient has normal *CYP2C19* metabolic activity, she has reduced *CYP2D6* metabolic activity, which will decrease her ability to metabolize amitriptyline. She also has a DDI, as both diphenhydramine and escitalopram further inhibit her *CYP2D6* activity. Both the drug-gene and DDIs are expected to lead to higher than expected levels of amitriptyline. Based on these factors, she was at higher risk for developing adverse events on amitriptyline. The initial therapy of 10 mg was likely too low to precipitate an adverse event, but 30 mg nightly increases her risk and requires monitoring. Although her headaches improved during amitriptyline therapy, she was concerned about side effects and discontinued treatment.

Genetic variants in *CYP2C9*, *VKORC1*, and *CYP4F2* contribute to warfarin dosing. Both her *VKORC1* and *CYP2C9* genotypes are associated with significantly increased sensitivity to warfarin. These genotypes explain the low maintenance dose (1–2 mg daily) required for her to maintain a therapeutic INR. Technically, her *CYP4F2* *1/*3 genotype would counterbalance the predicted effects of her *VKORC1* and *CYP2C9* genotypes, suggesting an increase in warfarin dose. However, the contribution of *CYP4F2* genotype to the variance in stable warfarin dose among patients of European ancestry is less than (~10%) that of *VKORC1* (~30%) and *CYP2C9* (~20%). The FDA drug label for warfarin recommends dose reduction to below 2 mg daily in individuals with this *CYP2C9* and *VKORC1* genotype combination.

In retrospect, genotype-guided recommendations support her present dose of anticoagulant and have potentially improved the management of her restless legs syndrome and headaches. Warfarin maintenance treatment is ongoing by alternating between 1 mg and 2 mg daily while the patient is preparing for possible total right knee replacement.

Clinical vignette 3: venlafaxine

A 35-year-old White man presented to a primary clinic to establish care and treatment for anxiety. He reported “full blown panic attacks” which began years ago. He received psychiatric services and was treated with selective serotonin reuptake inhibitors (SSRIs) and a benzodiazepine for a short period. After a new wave of anxiety, he was prescribed venlafaxine, a serotonin-norepinephrine reuptake inhibitor (SNRI) at 37.5 mg daily, a low starting dose which is appropriate for antidepressant therapy initiation. The expected course of improvement in his symptoms and possible side effects of venlafaxine, including potential thoughts of suicide, were discussed. If the patient experienced side effects he was encouraged to stop taking venlafaxine immediately and notify the prescriber.

The prescription of venlafaxine prompted the trial team to contact the patient regarding enrollment, which resulted in pharmacogenetic testing. Eight days after starting venlafaxine, the patient contacted his healthcare provider to advise that while the venlafaxine seemed to help somewhat with his anxiety, he did not “feel like himself.” Consequently, the patient decided to stop taking venlafaxine. The provider reviewed the patient’s genotyping report with recommendations from the INGENIOUS adjudication committee, noticed his *CYP2D6* genotype, attributed the side effects to his genotype, agreed with the patient to stop taking venlafaxine, and prescribed an alternative anxiolytic (clonazepam 5 mg twice daily). Two months later, he reported that his relationships were “better” and he is very productive at work.

Pharmacogenetic testing revealed that this patient has the *CYP2D6* *4/*10 genotype which predicted a reduced/intermediate metabolizer status. Reduced *CYP2D6* function will affect this patient’s ability to metabolize as many as 25% of commonly prescribed drugs, including antidepressants, antipsychotics, analgesics, antitussives, beta adrenergic blocking agents, antiarrhythmics and antiemetics [4]. Based on the patient’s *CYP2D6* metabolizer status, he has a decreased ability to metabolize venlafaxine. Knowing his metabolizer status explains the patient’s side effects to the medication and informed prescribing decisions.

Table 1:**Glossary of terms**

1. CYP: abbreviation for Cytochrome P450 enzymes which is a super family of enzymes involved in drug disposition
2. Pharmacogenomics: the study of the role of the genome (all the genes) in response to drugs/medicines. This term is often used interchangeably with pharmacogenetics.
2. Pharmacogenetics: usually refers to the study of how DNA variation in a single or few genes influences the response to a single drug/medicine
4. Substrate: the compound/medicine that is acted on, through binding (interaction), with the enzyme (in this case CYP enzymes) and is converted into an active or inactive form (metabolite)
5. Metabolite: 1) the product formed through the interaction of a compound/medicine with an enzyme (in this case CYP enzymes) and 2) a substance essential for a specific metabolic process
6. Prodrug: in the administered form, the compound is pharmacologically inactive and through interaction with a CYP or other enzyme, the compound is activated to have therapeutic effect
7. Inhibitor: a compound/molecule/medicine that decreases the activity of an enzyme (in this case CYP enzyme)
8. Inducer: a compound/molecule/medicine that affects gene expression in a way that increases the activity of an enzyme (in this case CYP enzyme)
9. Allele: one of several alternative forms of the same gene, at the same place of a chromosome, which is the result of a variant in the DNA sequence
10. Reference allele: (typically) refers to an unaltered DNA sequence which results in not increased nor decreased ('normal') function of the drug-metabolizing enzyme
11. Genotype: an individual's combination of two alleles
12. Phenotype: the set of observable characteristics of an individual resulting from the interaction of the individual's genotype with the environment

Table 2:

Drug-gene interactions at the time of genotype-guided dosing in three clinical vignettes

Case specific medications at the time of genetic testing	Relevant genotype	Predicted metabolizer status	Case specific recommendations based on drug-gene-interactions
Case #1			
clopidogrel	CYP2C19 *17/*17	ultra-rapid metabolizer	increased risk of bleeding
Case #2			
amitriptyline	CYP2D6 *4/*41	reduced/intermediate metabolizer	increased risk of toxicity
	CYP2C19 *1/*1	normal metabolizer	
escitalopram	CYP2C19 *1/*1	normal metabolizer	
warfarin	CYP2C9 *2/*3	poor metabolizer	increased risk of bleeding
	VKORC1 rs9923231 A/A	poor metabolizer	increased sensitivity
	CYP4F2 *1/*3	reduced/intermediate metabolizer	
Case #3			
venlafaxine	CYP2D6 *4/*10	reduced/intermediate metabolizer	increased risk of toxicity